Reconsideration of the application is requested in light of the following remarks.

REMARKS

I. Claim Status. Claims 34-47, 49-54, 59 and 60 are pending and have been examined. A copy of the pending claims is enclosed for the Examiner's convenience.

II. Claim Rejections. The rejections are summarized and addressed as follows.

Claims 34-36, 39, 43, 49, 59 and 60 stand rejected for obviousness-type double patenting over claims 3, 7, 8 and 13 of U.S. Patent No. 5,792,748 ("the '748 patent") in view of Werning et al. (Arch. Ontolaryngol. Head Neck Surg., 1995, 121:783-789) ("Werning et al.") and Cincotta et al. (Cancer Res., 1994, 54:1249-1258) ("Cincotta et al.") as evidenced by Molitch (Endocrinol. Metab. Clin. North Am., 1992, 21:877-901 ABSTRACT ONLY) ("Molitch").

Claims 34-37, 43, 49 and 59 stand rejected for obviousness-type double patenting over claims 12-13, 28 and 30 of U.S. Patent No. 6,071,914 ("the '914 patent"), in view of Werning et al. and Cincotta et al. as evidenced by Molitch.

Claims 34-47, 49-54, 59 and 60 stand rejected under 35 U.S.C. § 103(a) over the '748 patent and/or '914 patent, in view of Werning et al. and Cincotta et al. as evidenced by Molitch.

All the rejections are respectfully traversed. Applicants continue to maintain that the references cited by the Examiner do not, either individually or in combination, suggest the combination of treating tumors by adjusting the daily plasma prolactin profile of a tumor bearing mammal by administering a prolactin enhancer at appropriate time intervals of day such that the adjusted daily plasma prolactin profile of the tumor bearing mammal conforms to or approaches

the normal prolactin profile for healthy members of the same species and sex as the mammal and subjecting the tumor cells to PDT using a benzophenoxazine-analog, as claimed.

The Examiner asserts that Applicants have argued and discussed the references individually without addressing the combined teaching. Applicants respectfully disagree. The present obviousness-type double patenting and obviousness rejections cannot stand, precisely because the combined teachings of the references would not have suggested the instant claims to one of ordinary skill in the art. In particular, one of ordinary skill in the art would not find any motivation to combine either the claims or specification of the '748 patent or '914 patent with Werning et al., as evidenced by Molitch.

Applicants draw the Examiner's attention to the fact that the instant claims are not merely drawn to treating tumors by administration of a prolactin enhancer and PDT. The claims are rather drawn to PDT in combination with adjusting the daily plasma prolactin profile of the tumor bearing mammal to approach the profile of a normal mammal, by administering a prolactin enhancer at appropriate time intervals (see claim 34).

The combined references fail to include either the motivation or the expectation of success to combine the methods. The Examiner concedes that neither the '748 patent nor the '914 patent includes any suggestion to treat tumors by combining prolactin rhythm resetting using a prolactin enhancer, as disclosed and claimed therein, with PDT. The Examiner seeks to provide a motivation for combining prolactin rhythm resetting therapy and PDT by stating that "Werning (sic "Werner") *et al.* clearly suggest to one of ordinary skill a reasonable expectation of success because "tumors exposed to PDT alone showed 80% to 90% tumor regression with regrowth in most animals within 20 days"; however, "tumors treated with the **prolactin enhancer** plus PDT demonstrated 100% tumor regression without regrowth (see Werning *et al.*,

abstract)" (bold emphasis added). Contrary to the Examiner's assertion, however, Werning et al., make no such statement. Werning et al. state instead that metoclopramide hydrochloride improves PDT in nude mice.

Hence, all discussion in Werning et al. is restricted to metoclopramide and the effects directly attributable to metoclopramide. There is simply no disclosure in Werning et al. that the effect obtained by combining metoclopramide administration and PDT is related in any way to plasma prolactin levels. Prolactin is not mentioned even once in Werning et al. Hence, Werning et al. suggest that metoclopramide can sensitize tumor cells to chemotherapy and radiation therapy, that metoclopramide has the ability to damage DNA directly and inhibit the repair of DNA damage caused by other agents and that metoclopramide has been reported to increase the distribution of blood flow to tumors. Werning et al fail to make any suggestion, however, that these effects are mediated through plasma prolactin levels. Accordingly, Werning et al. fail to include any motivation or suggestion that metoclopramide be used to adjust the daily plasma prolactin profile of a tumor bearing mammal, in combination with PDT.

Accordingly, as noted by the Examiner, although Werning et al. set forth that "administering metoclopramide in combination with PDT may be a promising approach to the management of head and neck cancer," the Examiner is incorrect to state that "Werning et al. ...does not preclude one of ordinary skill in the art from clearly comprehending the obvious synergism that occurs when PDT is combined with the prolactin enhancer." When there is no evidence or suggestion that the effects observed in Werning et al. are due to metoclopramide's effect on plasma prolactin levels, there can be no "obvious synergism" to observe between PDT a prolactin enhancer. Furthermore, where Werning et al. is completely silent as to metoclopramide's effect on plasma prolactin levels, there can be no suggestion that

metoclopramide be administered in a manner to adjust the daily plasma prolactin profile of a tumor bearing mammal, in combination with PDT.

Additionally, the references cited by the Examiner teach affirmatively, both explicitly and implicitly, that the effect of metoclopramide is NOT through its effects on prolactin levels. It is therefore improper to combine the '748 patent or '914 patent with Werning et al. because the '748 patent and '914 patent are explicitly directed only to methods of treating tumors by resetting the daily plasma prolactin profile of a tumor bearing mammal to approach or conform the normal daily plasma prolactin profile for healthy members of the same species and sex of the mammal, whereas Werning et al., as evidenced by Molitch et al., teach away from resetting the prolactin profile of the tumor bearing mammal to approach the prolactin profile of a normal mammal.

Hence, Werning et al. teach that there is a direct dose response correlation between the metoclopramide dose and tumor ablation. Doses of 16, 32 and 48 mg/kg, respectively, showed the greatest efficacy in treating tumors, when combined with PDT. Accordingly, Werning et al. teache that the metoclopramide dose should be maximized to effect treatment in combination with PDT. Adjusting the plasma prolactin profile of a tumor bearing mammal to approach the profile of a normal mammal, however, requires that a prolactin enhancer not be administered to maximize prolactin levels. Such administrations would not adjust the plasma prolactin profile of a tumor bearing mammal. This type of administration would lead to uniformly high levels of plasma prolactin, in direct conflict with the teaching of the '748 patent and '914 patent, and in direct conflict with the instant claims. Hence, the disclosure of Werning et al. teaches away from the disclosure of '748 patent and '914 patent.

Applicants' assertion that the disclosure of Werning et al. is incompatible with the teaching of the '748 patent and '914 patent is supported by Molitch. Hence, Molitch states that, "Pathologic increases of PRL [prolactin] owing to hypothalamic dysregulation occur with a variety of medications, including...metoclopramide." (emphasis added) Accordingly, Molitch does not evidence that metoclopramide, as administered in Werning et al., is a prolactin enhancer that may be used in combination with '748 patent and '914 patent to arrive at the instant claims. To the contrary, Molitch teaches explicitly that metoclopramide cannot be used to reset the daily plasma prolactin profile of a tumor bearing mammal to approach the profile of a normal mammal. Hence, Molitch and Werning et al. teach away from each of the '748 patent, the '914 patent and the instant claims. Accordingly, it is improper to combine Werning et al., as evidenced by Molitch, with the '748 patent or '914 patent to arrive at the instant claims.

Accordingly, for all the reasons set forth above, Applicants submit that none of the prior art cited by the Examiner suggests any motivation or benefit to treating tumors by the combination of adjusting the plasma prolactin profile of a tumor bearing mammal to approach or conform to the profile of a healthy mammal with PDT. Applicants continue to maintain that the Examiner has failed to establish a prima facie case of obviousness based upon the prior art. Both the suggestion of making the present invention and a reasonable expectation of success must be founded in the prior art, not in Applicants' disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529, 1531 (Fed. Cir.1988). For the reasons set forth above, Applicants assert that neither the '748 patent nor '914 patent, either alone or in combination with Werning et al., contains the required suggestion to treat tumors by combining the resetting of a plasma prolactin profile with PDT. Accordingly, Applicants continue to respectfully maintain that the Examiner has either relied on the Applicants' disclosure or applied an obvious to try standard as the

rationale for combining the cited references to arrive at the presently claimed invention. Neither reliance on Applicants' disclosure nor obvious to try is a valid test of patentablility. *In re Dow Chemical Co.*, 837 F.2d 469, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir.1988); *In re O'Farrell,* 853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir.1986); *In re Geiger,* 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987). Hence, the present rejections should be withdrawn.

Objective Evidence of Non-obviousness

Applicants further continue to traverse the obviousness-type double patenting and obviousness rejections on the grounds that treating tumors by combining the resetting of a plasma prolactin profile with PDT leads to unexpected results, compared to the results obtained when each method is used alone. The unexpected results by combining these methods were set forth in Applicants' response to the prior Office Action. The results are objective evidence that the claimed methods are non-obvious.

As set forth above and as further evidenced by Molitch, the metoclopramide treatment set forth in Werning et al. would not result in adjusting the daily plasma prolactin level of a tumor bearing mammal to approach or conform to the profile of a healthy animal. Accordingly, Werning et al. does not and cannot demonstrate or suggest an unexpected efficacy would be achieved by the combination of administering a prolactin enhancer to adjust a daily plasma prolactin level with PDT. Accordingly, the results set forth in the instant application constitute unexpected results that are not found or suggested in the prior art.

For the reasons set forth above, Applicants respectfully suggest that claims 34-47, 49-54, 59 and 60 are not obvious over either the specification or claims of the '748 patent or '914 patent in view of Werning et al. and Cincotta et al., as further evidenced by Molitch.

Accordingly, Applicants respectfully request reconsideration of 34-47, 49-54, 59 and 60 and withdrawal of all rejections of these claims for obviousness-type double patenting and under 35 U.S.C. § 103 (a).

III. Ownership/Inventorship of U.S. Patent No. 6,071,914. The Examiner has asked for clarification of the ownership and inventorship of U.S. Patent No. 6,071,914. As set forth in the response to the prior Office Action, U.S. Patent No. 6,071,914 is owned by Ergo Science Incorporated and The Board of Supervisors of Louisiana State University and Agricultural and Mechanical College. Anthony H. Cincotta and Albert H. Meier are joint inventors of each claim in the '914 patent. The present application is owned by The General Hospital and the Rowland Institute for Science, which is now part of Harvard University. The named inventors, Anthony H. Cincotta and Louis Cincotta are joint inventors of each pending claim of the present application.

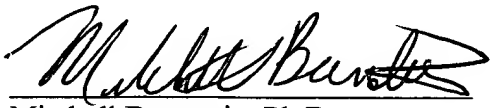
Applicants respectfully submit that the non-obviousness of the instant claims over the prior art of record renders further inquiry into inventorship and ownership of the instant invention and the invention claimed in the '914 patent moot. Should the Examiner wish further information regarding these issues, however, he is requested to contact Applicant's agent at the number listed below.

CONCLUSION

Therefore, in view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



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All persons associated with the filing and prosecution of a patent application have a duty to disclose to the Patent Office any information, including known prior art, which may be material to the examination of the application. Material information includes prior art that could be used to challenge patentability of a claim, or that refutes or is inconsistent with a position the applicant takes in arguing an examiner's rejection or asserting patentability (such as a post-filing peer reviewed publication that is contrary to the invention, or the discovery of an error in the experimental data on which the application is based). Failure to disclose such information gives rise to a substantial risk that any patent granted on the application will be unenforceable or invalid.

The applicant(s) for a patent satisfy this duty by disclosing all material information to the attorney or agent prosecuting the application. Therefore, please provide us with copies of all prior art of which you are now aware or you become aware in the future, including references uncovered during prosecution of foreign counterparts of the present application and related U.S. applications, as well as filing details and copies of U.S. application directed subject matter similar to this application that we are not aware of.

The Patent Office will consider any information disclosed within three months of the filing date of this application or prior to the mailing date of the first Office Action. Thereafter, a government fee has to be paid to have prior art considered, unless we can certify that all of the cited references first became known to the applicant, the attorney, or anyone else involved in preparation and/or prosecution of the application, or were first cited in a foreign counterpart of this patent application within three months of the disclosure date. Furthermore, any references should be submitted within 30 days of one of the foregoing parties becoming aware of it to avoid any implication of undue delay in prosecution.

To prepare an Information Disclosure Statement, we need copies of all references and other material information. It is usually less expensive if you provide us with copies of non-patented references. For each reference which is not in English, we also need a concise explanation of its relevance. This explanation must be from one of the inventors or of a person involved in the preparation or prosecution of this application, whoever is most knowledgeable about the content of the reference. If the non-English reference was cited in a foreign counterpart of this application, we need only provide a copy and an English translation of the search report or office action in which the reference was cited. You need not provide an English translation, unless you or an inventor already has one, or if one is readily available.

Please bring all currently known information to our attention as soon as possible.